

REMARKS

Claims 1, 2, 4-8, 10-24, 26-28 are pending. Claims 17-24, 26, and 27 are withdrawn. Claims 3, 9, and 25 are canceled.

Claim 1 has been amended to recite "wherein said displacing comprises flowing said wash fluid across said surface in a manner sufficient to produce a stratified fluid interface that moves across said surface" in step d) and "in a manner sufficient to produce a stratified fluid interface that moves across said surface" in step h). Support for this amendment may be found on page 32, lines 17-33 of the specification and in Claim 9 as originally filed.

Claims 10 and 11 have been amended to change their dependency to Claim 1.

No new matter is added.

In view of the following remarks, the Examiner is requested to withdraw the rejections and allow claims 1, 2, 4-8, 10-16 and 28, the only claims pending and currently under examination in this application.

Claim Rejections - 35 USC § 102 Bass

Claims 1, 16, and 28 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Bass (USPN 6,420,180). The Applicants respectfully traverse this rejection.

Since the original Claim 9 is not rejected over Bass, this rejection has been rendered moot by the incorporation of Claim 9 into Claim 1.

Accordingly, Claim 1 and its dependents cannot be rendered anticipated by Bass and the Applicants respectfully request the withdrawal of this rejection.

Claim Rejections - 35 USC § 103 Bass and Anderson

Claims 2 and 4-15 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Bass (USPN 6,420,180) in view of Anderson et al. (USPN 5,186,824). The Applicants respectfully traverse this rejection.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. See, e.g., *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491

F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. See, e.g., *KSR* at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing *KSR*. Further, the Supreme Court in *KSR* also stated that that “a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.” *KSR* at 1740; emphasis added. As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

In making this rejection, the Examiner acknowledges that “Bass does not provide any information on wash fluid or deblocking fluid or wherein the method utilizes a flow cell” (page 3 of Final Office Action dated 7/21/08) and cites Anderson to remedy Bass’s deficiency. The Examiner further asserts that one of skilled in the art would have been motivated to combine the references in the manner because of expected benefits and expanded applications (page 5 of Final Office Action dated 7/21/08).

Claims 2, 4-8, and 10-15 further describe the *in situ* fabrication process of Claim 1. They are also ultimately dependent on Claim 1 and thus contain all the limitations of Claim 1.

For reasons submitted below, the Applicants contend that in view of the cited references, one of skilled in the art would not have arrived at the rejected claims. For example, “removing deblocking fluid from said deblocked surface by [...] flowing said wash fluid across said surface in a manner sufficient to produce a stratified fluid interface that moves across said surface,” as required by the rejected claims, cannot be taught or suggested by the cited art.

One of the reasons why one of skilled in the art would not have arrived at “removing deblocking fluid [...] by [...] flowing said wash fluid [...] in a manner sufficient to produce a stratified fluid interface that moves across said surface” is that Bass and Anderson teach very different protocols and there is no teaching or suggestion to modify Bass in order to arrive at the rejected claims. Briefly, Bass teaches a method of attaching different moieties to various discrete locations on an addressable array. Bass, however, is completely silent on “removing deblocking fluid

[...] by [...] flowing said wash fluid [...] in a manner sufficient to produce a stratified fluid interface that moves across said surface."

Anderson, on the other hand, teaches a batch reactor for synthesizing oligonucleotides on controlled-pore glass beads that are suspended in the reactor during fluid exchange. According to the passages cited by the Examiner, column 12 and Figs. 2A-2D in Anderson "illustrate the behavior of liquids that are introduced sequentially in increasing density to the core edge of the rotor body during rotation" (column 12, lines 28-30). Anderson further teaches that the "interface between the light solution and the dense solution assumes the configuration of a parabola of rotation" (column 12, lines 40-43). As such, Anderson teaches that the rotation of the rotor fluid creates an interface during sequential introduction of liquids.

As apparently clear, the methods of Bass and Anderson are very different, the former directed to synthesizing different moieties at various discrete locations on an addressable array, while the latter is directed to a batch synthesis reaction, in which *in situ* fabrication of different oligonucleotides on addressable locations would be impossible. As such, there can be no teaching or suggestion as to how one might modify Bass's *in situ* fabrication method to accommodate Anderson's teaching of fluid displacement in a rotating reactor.

Another reason why one of skilled in the art would not have arrived at the rejected claims is that since Anderson's method of oligonucleotide synthesis occurs on beads suspended in a rotor, there is no fluid interface that moves across a surface of an addressable array. As such, there is also no teaching or suggestion of "a stratified fluid interface that moves across said surface [of an addressable array]." Accordingly, without the hindsight provided by the Applicants, one of skilled in the art would not have combined the cited art to arrive at "removing deblocking fluid [...] by [...] flowing said wash fluid [...] in a manner sufficient to produce a stratified fluid interface that moves across said surface."

Moreover, contrary to the statements the Examiner has made, there is no support that the combination would result in "expected benefits and expanded applications," asserted by the Examiner as a reason for one of skilled in the art to make such a combination. First, it is unclear as to what those benefits and applications are that would have led one of skill in the art to arrive at the rejected claims. Second, since each reference is directed to a different type of oligonucleotide

synthesis, one of skill in the art would not have perceived any benefit or applications resulting from combining a method for an addressable array with a batch synthesis reactor.

Furthermore, a careful consideration of the field of array synthesis reveals that the much of the teaching around the priority date of the instant application comprises drying steps in between wash steps and is completely devoid of the element of "removing deblocking fluid from said deblocked surface by [...] flowing said wash fluid across said surface in a manner sufficient to produce a stratified fluid interface that moves across said surface." Certain patents are briefly discussed below to illustrate the prevalent practice of air drying in the field of array synthesis and the lack of teaching of "removing deblocking fluid from said deblocked surface by [...] flowing said wash fluid across said surface in a manner sufficient to produce a stratified fluid interface that moves across said surface."

On such reference is Glazer et al. (USPN 6,824,866), in which the performance of an array substrate was tested by synthesizing fluorescein phosphoramidite onto the substrate. In column 22, lines 43-45 of Glazer, the substrates are "deprotected [...]" and blown dry with dry nitrogen."

In Blanchard et al. (USPN 6,028,189) and Blanchard et al. (USPN 6,419,883), the methods taught in both references require "drying in a stream of dry nitrogen" in columns 12 and 38, respectively.

Schermer et al. (USPN 6,485,918) teaches an apparatus for array synthesis that performs "automatic washing and drying." The method taught by Schermer also involves jetting wash solutions and vacuum or gas-stream drying (column 8, lines 47-59).

Gamble et al. (USPN 5,981,733), a reference cited in the previous response filed 9/22/08, teaches that the array substrate is to be "dried with a stream of compressed gas [...] to remove any unreacted deprotect reagent" (column 13, lines 5-15).

In view of the above-cited patents, the prevalent teachings in the art of array synthesis employ air drying and are completely silent on "removing deblocking fluid from said deblocked surface by [...] flowing said wash fluid across said surface in a manner sufficient to produce a stratified fluid interface that moves across said surface." As such, without the hindsight provided by the Applicants' application, one

of skill in the art would not have any reason to combine Bass and Anderson teachings in the manner suggested by the Examiner to arrive at the rejected claims.

In addition to the fact that Anderson cannot remedy Bass's deficiency for not teaching or suggesting "removing deblocking fluid [...] by [...] flowing said wash fluid [...] in a manner sufficient to produce a stratified fluid interface that moves across said surface," as recited in Claim 1 and that all claim rejections should be withdrawn for this reason alone, the Applicants further note that the combination of Bass and Anderson also does not teach or suggest the following dependent claims.

With respect to Claim 10, the Examiner attempts to support the rejection of Claim 10 by citing column 5, lines 15-27, column 14, lines 44-53, and column 21, lines 30-65 in Anderson. The Applicants traverse this rejection of Claim 10.

As discussed in the previous response filed 9/22/08, nowhere is there a teaching or suggestion related to flow rate in Anderson. The cited passages only mention fluid flow and how valves control fluid flow. In maintaining this rejection, the Examiner asserts that fluid flow is equivalent to flow rate and states that one of skilled in the art would have been motivated to adjust the flow rate based on Anderson. The Applicants contend the fluid flow is not the same as flow rate and since Anderson is completely silent on the subject of flow rate, there can be no teaching or suggestion to adjust the flow rate. Withdrawal of the rejection of Claim 10 is respectfully requested.

With respect to Claim 11, the Applicants contend that neither Bass nor Anderson teaches or suggests "sensing movement of the stratified fluid interface." In maintaining this rejection, the Examiner points to column 12, lines 28-67 in Anderson and alleges that any movement of fluid would be construed to be equivalent to "sensing movement of the stratified fluid interface."

However, claim construction must not be made in a vacuum but must be considered from the point of view of one of skilled in the art and in the context of the specification.¹ Based on how one of skilled in the art would interpret "stratified fluid interface" and page 32 of the specification, it is clear that interface cannot be construed as any fluid movement. An interface exists as a front between two

¹ *E.g.*, *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1477 (Fed. Cir. 1998), *Innova*, 381 F.3d 1116; *Gemstar-TV Guide Int'l, Inc. v. Int'l Trade Comm'n*, 383 F.3d 1352, 1364 (Fed. Cir. 2004); *Vitronics*, 90 F.3d at 1582-83, *Markman*, 52 F.3d at 979-80.

different fluids. The cited passages in Anderson are completely silent on "sensing movement of the stratified fluid interface." Since no teaching or suggestion is found anywhere in the cited references, rejection of Claim 11 should be withdrawn.

With respect to Claim 12-14, the Applicants submit that none of the cited references teach or suggest performing the claimed method "in a flow cell." In maintaining this rejection, the Examiner asserts that Anderson teaches flow cell chambers (bottom of page 6 of Advisory Action dated 10/20/08). However, the Applicants contend that Anderson's rotating rotor cannot be a flow cell based on functional embodiments of the rejected claims construed by one of skilled in the art. An addressable array cannot be mounted or placed in a rotating rotor. Contact printing to "at least a first location and a second location of a surface of a substrate" would also be impossible. Although Bass teaches "a housing [that] may include a closed chamber," Bass is completely silent in contacting the "deblocking fluid" or "displacing the deblocking fluid with a wash fluid" in the enclosed chamber. Hence, neither Bass nor Anderson can teach the element of "a flow cell," as required by Claims 12-14.

Not only is there no teaching or suggestion to combine the references in the manner suggested by the Examiner, the combination of the references would also result in a change of the principles of operation or render them inoperable. Under current law, such logic cannot be used to establish a *prima facie* case of obviousness.²

Even if one were to combine or modify the teachings in an attempt to comport with the rejected claims, one of skilled in the art would resort to a rotating rotor as taught by Anderson while introducing fluids sequentially in increasing density to achieve the "stratified fluid interface," as required by Claim 1. However, combining this method of achieving a stratified fluid interface with the *in situ* array fabrication of Bass, one would end up having an addressable array inside a rotating rotor. An addressable array cannot exist in suspension nor can deposition at discrete location on an array be operable if the substrate were to be enclosed in Anderson's rotor. As such, the combination would render either Bass's method or Anderson's method inoperable or change their principles of operation.

² *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); MPEP 2143.01 VI; *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); MPEP 2143.01 V

In view of the foregoing discussion, the combination of Bass and Anderson cannot render the rejected claims obvious. Considering the art of array synthesis around the time of filing and the teachings of Bass and Anderson, nothing taught or suggested would have led one of skilled in the art to arrive at the rejected claims without the hindsight provided in the instant application. The Applicants further submit that dependent claims 10-14 are also nonobvious over Bass and Anderson for additional reasons set forth above. Lastly, the proposed modification to modify Bass or Anderson to comport with the rejected claims would either change the principle of operation or render the methods taught inoperable. As such, the combination of these cited references cannot be used to establish a *prima facie* case of obviousness. Accordingly, the Applicants request that the rejection be withdrawn.

CONCLUSION

In view of the amendments and remarks above, the Applicants respectfully submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret Field at (650) 327-3400.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078.

Respectfully submitted,

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